REMARKS

The Claim Amendments

Claim 23 has been amended to recite a method of inhibiting ERK or AKT activity in selected biological samples *in vitro*. Support for this amendment is found in the specification on page 42, lines 4 to 8.

Claim 27, *inter alia*, and claim 28 have been amended to recite a method of treating a cancer selected from breast cancer, colon cancer, kidney carcinoma, lung cancer, melanoma, ovarian cancer, pancreatic cancer, or prostate cancer. Support for these amendments is found in the specification on page 45, line 10, to page 46, line 13 and in the claims as originally filed.

Claim 27, *inter alia*, and claim 33 have been amended to recite a method of treating Alzheimer's disease. Support for these amendments is found in the specification on page 45, line 10, to page 46, line 13 and in the claims as originally filed.

Claim 27, *inter alia*, and claim 35 have been amended to recite a method of treating cardiovascular disease selected from stroke, restenosis, cardiomegaly, atherosclerosis, myocardial infarction, or congestive heart failure. Support for these amendments is found in the specification on page 45, line 10, to page 46, line 13 and in the claims as originally filed.

Claim 27, *inter alia*, and claim 38 have been amended to recite a method of treating asthma. Support for these amendments is found in the specification on page 45, line 10, to page 46, line 13 and in the claims as originally filed.

Claims 29, 31-21, 34, 36, and 39-43 have been canceled.

None of the amendments contain new matter. Their entry is requested.

Applicants reserve the right to pursue canceled subject matter in the application or in an application claiming priority therefrom.

The Response

Rejection under 35 U.S.C. § 112

The Examiner has rejected claims 23 and 27-41 under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement. In particular, the Examiner asserts that the specification does not reasonably provide enablement for (*i*) a method of inhibiting ERK or AKT activity in a biological sample (claim 23); (*ii*) a method of treating neurological

disorders generally or specific neurological disorders, such as, for example, Alzheimer's disease, Parkinson's disease, ALS, or Huntington's disease (claims 27 and 33-34); (*iii*) a method of treating inflammatory disorders, such as, for example, asthma (claims 27 and 38-39); (*iv*) a method of treating cardiovascular disease generally or individual cardiovascular disorders, such as, for example, stroke, restenosis, cardiomegaly, atherosclerosis, myocardial infarction, or congestive heart failure (claims 27 and 35-36); or (*v*) a method of treating cancer generally or a cancer selected from a list of specific cancers (claims 27-29).

Regarding item (*i*), claim 23 has been amended to incorporate the term "*in vitro*" to and to recite specific biological samples in which ERK activity is inhibited, thus clearly differentiating the inhibition of ERK in a biological sample from the *in vivo* inhibition of ERK for the treatment of disease. The specification provides ample support for the inhibition of ERK and AKT3 kinase (see, e.g., Tables 6 and & on pages 59-63) and this amendment obviates the Examiner's implied objection to claim 23 as reciting a method of treating disease in general by inhibiting AKT or ERK.

Regarding item (*ii*), amended claims 27 and 33 recite a method of treating Alzheimer's disease. At the time of the invention, it was known that the neuronal microtubule-associated protein tau becomes highly phosphorylated, loses its binding properties, and aggregates into paired helical filaments in patients with Alzheimer's disease. In one study, the physiological phosphorylation of endogenous tau protein in metabolically labeled human neuroblastoma cells and in Chinese hamster ovary cells stably transfected with tau was measured and 17 phosphorylation sites were identified, comprising 80-90% of the total phosphate incorporated. See the abstract of Illenberger et al., *Mol. Biol. Cell* 9(6): 1495-512, 1998 (hereafter, "Illenberger"). ERK2 was known at the time of the invention to mediate the phosphorylation of tau. See page 1057, paragraph 2, of Raghunandan et al., *Biochem. Biophys. Res. Commun.* 215(3):1056-66, 1995 (hereafter, "Raghunandan"). Further, Fukunaga et al., *Mol. Neurobiol.* 16(1): 79-95, 1998 (hereafter, "Fukunaga") have postulated that ERKs are attractive candidates to mediate morphological differentiation and promote survival in neurons, and their inhibition may mediate physiological and pathological events such as Alzheimer's disease and cerebral ischemia. See the abstract of Fukunaga. Taken together with the specification, Illenberger, Raghunandan, and Fukunaga clearly show that there is a reasonable correlation between the inhibitors of the invention, their ERK2 inhibitory activity, and the use of these compounds to treat Alzheimer's disease.

Regarding item (*iii*), amended claims 27 and 38 recite a method of treating asthma in a patient in need thereof by compounds of the invention. The role of ERK in allergy and asthma was established at the time of the invention, as it was known that the survival and apoptosis of eosinophils is of pivotal importance for controlling allergic diseases, such as asthma. See page 36 of Chang et al., *Cell Immunol.* 203(1):29-38, 2000 (hereafter "Chang") showed that a MAP/ERK kinase inhibitor was partly able to block augmentation of eosinophil viability in cell culture studies. Taken together with the specification, Chang clearly shows that there is a reasonable correlation between the inhibitors of the invention, their ERK2 inhibitory activity, and the use of these compounds to treat allergy/asthma.

Regarding item (*iv*), amended claims 27 and 35 recite a method of treating a cardiovascular disease selected from stroke, restenosis, cardiomegaly, artherosclerosis, myocardial infarction, or congestive heart failure in a patient in need thereof by compounds of the invention. The role of ERK in cardiovascular disease has been demonstrated. For instance, the chronic activation of tyrosine phosphorylation, in particular the redistribution and phosphorylation of ERK1/ERK2 in the brain tissue of ischemic stroke victims, was known at the time of the invention. See page 2762, column 2, to page 2763, column 1, of Slevin et al. in *Neuroreport* 11(12): 2759-64, 2000 (Exhibit E; hereafter "Slevin"). Further, the intravenous administration of an ERK inhibitor afforded brain protection against forebrain ischemia and focal cerebral ischemia in an animal model. See the abstract and page 11572, column 2, in Namura et al., *Proc. Natl. Acad. Sci. U S A* 98(20): 11569-74, 2001 (Exhibit F; hereafter "Namura").

In addition, the role of ERK in cardiac hypertrophy, a condition known to be associated with congestive heart failure and myocardial infarction, was established at the time the invention was made. Markers indicative of hypertrophy could be suppressed by a MEK/ERK inhibitor in stimulated neonatal rat cardiomyocytes. See the abstract and page H1641, right column, to page H1642, left column, of Kodama et al. in *Am. J. Physiol. Heart Circ. Physiol.* 279(4): H1635-44, 2000 (hereafter, "Kodama"). Taken together with the specification, Slevin, Namura, and Kodama, clearly show that there is a reasonable correlation between the inhibitors of the invention, their ERK2 inhibitory activity, and the use of these compounds to treat the cardiovascular diseases recited in amended claims 27 and 35.

Regarding item (*v*), amended claims 27 and 28 recite a method of treating a cancer selected from breast cancer, colon cancer, kidney carcinoma, lung cancer, melanoma, ovarian

cancer, pancreatic cancer, or prostate cancer. A link between ERK kinase activity and various cancers had been established at the time of the invention. For instance, it was known that MAP/ERK kinases play a pivotal role in mitogenic signal transduction and that the aberrant activation of signal transducing molecules, such as Ras and Raf-1, via MAP/ERK kinases was linked with the recited cancers. See, e.g., page 2, lines 11-19 of the specification. Constitutive activation of MAP/ERK kinases had been found in primary tumor cell lines derived from human pancreas, colon, lung, ovary and kidney. See the abstract of Hoshino et al., *Oncogene* 18: 813-22, 1999 (Exhibit K; hereafter, "Hoshino"). ERK had also been shown to be constitutively active in human melanoma tumor cell lines. See page 302, right column, of Kortylewski et al., *Biochem. J.* 357(Pt 1): 297-303, 2001 (Exhibit L; hereafter, "Kortylewski"). Additionally, it had been demonstrated that transforming growth factor beta-2 potently activates ERK2 in a human tumor cell line for breast cancer. See page 47, left column, in Frey et al., *Cancer Lett.* 117(1): 41-50, 1997 (Exhibit M; hereafter, "Frey"). Further, it was known that EGF and IGF-1 are potent mitogens that play a regulatory role in the proliferation of prostate cancer cells and that a monoclonal antibody against the EGF receptor abrogates p42/ERK2 activation in a human tumor cell line for prostate cancer. See page 231, right column, in Putz et al., *Cancer Res.* 59(1): 227-33, 1999 (Exhibit N; hereafter, "Putz"). Taken together with the specification, Kortylewski, Hoshino, Frey, and Putz clearly show that there is a reasonable correlation between the activation of ERK in various cancers, the use of an ERK inhibitor to inhibit cancer cell growth, and the use of the ERK inhibitors of the invention to treat the cancers recited in claims 27 and 28.

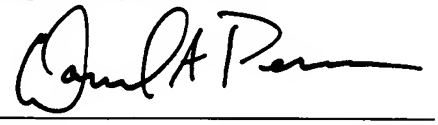
As discussed above, applicants have demonstrated that ERK and AKT3 inhibition is useful in the treatment of the diseases recited in amended claims 23, 27-28, 30, 33, 35, and 37-38. Further, for each of the therapeutic methods discussed above, a skilled artisan would be able to discern an appropriate dosage and method of use based upon the information provided in the specification (see page 48, line 4, to page 52, line 5) along with the general knowledge of one skilled in the art. Accordingly, one skilled in the art would find it reasonable to use the ERK/AKT3 inhibitors of the present invention for the treatment of the recited diseases without undue experimentation. Thus, the teachings of the specification, combined with the state of the art at the time of the invention, fully enable the claimed invention with respect to the aforementioned diseases. For all of the reasons set forth above,

applicants respectfully request that the Examiner withdraw her rejection over 35 U.S.C. § 112, first paragraph.

Conclusion

Applicants request that the Examiner enter the above amendments, consider the matters taken up in the remarks, and allow the claims to pass to issue. Should the Examiner deem expedient a telephone discussion to further the prosecution of the above application, Applicants request that the Examiner contact the undersigned.

Respectfully submitted,



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